DIAGNOSIS AND TREATMENT OF VIRAL INFECTIONS*

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GIVEN the universal skepticism about the natural history and treatment of many human viral infections, it is quite appropriate to question the usefulness of diagnosis and, in certain situations, the treatment of viral infections. For several decades now, the general perception has been that most viral infections are trivial, such as rhinovirus colds or clinically so apparent, such as chickenpox, measles, or herpes, that diagnostic testing is unnecessary, time consuming, and not cost effective. It can be argued that laboratory diagnosis does not help treatment of the patient, since most subjects are managed uneventfully regardless of the availability of laboratory diagnosis of specific etiology.

If all viral infections in childhood could be prevented by immunization at an appropriate age, there would be no need to provide routine diagnostic facilities or hospitalized care and specific antiviral therapy for seriously ill children with viral infections. Unfortunately, such hopes will remain unfulfilled for another few decades. Recent introduction of tissue and organ transplantation and such other treatment modalities as chemotherapeutic and immunosuppressive agents for maligancies and immunologically mediated disorders have significantly increased the life span and altered the quality of life for many patients who would not have otherwise survived. Prolonged survival of such immunologically compromised patients has added a diverse spectrum of new clinical syndromes of viral infections, not commonly seen previously in the normal host. Examples include potentially fatal infections with varicella zoster, herpes simplex, cytomegalovirus, and respiratory syncytial virus. In addition, new viral agents and new complications of old viruses and existing viral vaccines have been identified in recent years (Table

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I) in normal and immunocompromised host. More than 90% of human viruses known today were completely unknown at the end of the late 1940s, and only two viral vaccines for human use existed prior to 1960.

Since the introduction of several effective agents for treatment of viral infections, other arguments have been offered to foster use of viral laboratory diagnosis in association with specific antiviral therapy. Some of the benefits of establishing viral diagnosis are listed in Table II.

Respiratory Syncytial Virus

Infection with this agent is common worldwide and more than 80 to 85% of childhood population is infected by four years of age. The spectrum of disease following respiratory syncytial virus infection may range from mild asymptomatic upper respiratory infection to severe pneumonia, bronchiolitis, development of recurrent reactive airway disease, neonatal apnea, and death. Infection can be severe enough to require hospitalization (approximate rate 15-38/1000 infants/year). The infection is highly communicable with an attack rate ranging from 40 to 45% in family settings to 75 to 80% during epidemics.[1-3] It is estimated that the nosocomial infection rate with respiratory syncytial virus is about 25 to 30% during community outbreaks, necessitating prolongation of hospital stay by as many as two to five days. Hospitalized patients highly susceptible to development of severe disease and sometimes death following respiratory syncytial virus infection include those with congenital heart disease, bronchopulmonary diseases (bronchopulmonary dysplasia), prematurity, and the combined immunodeficiency syndromes.[4-6]

Several laboratory procedures are available for diagnosis of this infection (Table III). For any of these tests, it is necessary to consider speed, sensitivity, specificity, cost, and technical complexity relative to its impact on the diagnosis and treatment of respiratory syncytial virus infection. Information based on several years of laboratory experience with immunofluorescent antibody testing and tissue culture infectivity on specimens of nasophayrngeal smears suggests that immunofluorescent antibody testing is extremely rapid (seven hours), sensitive, and highly specific to detect respiratory syncytial virus antigen (Table IV). Experience with ELISA is limited. The procedure is rapid, requires less complex equipment, is not technically complex, and thus may be less costly than both tissue culture infectivity and immunofluorescent antibody testing.[7] However, it is not certain whether the sensitivity and specificity of ELISA is comparable to immunofluorescent an-

TABLE I. VIRAL DIAGNOSIS AND DISEASE MANAGEMENT*

1) Normal host
Rabies exposure
Congenital rubella prevention
Gestational herpes simplex virus
Herpes simplex virus immunization in the neonate
2) Compromised host
Cytomegalovirus, Herpes simplex virus, Varicella zoster virus, respiratory syncytial virus, measles, parvoviruses
3) Emerging new infections
Human immunodeficiency virus
Varicella zoster virus vaccine related illness
Live poliovaccine related illness

*These infections are neither trivial nor clinically obvious, and the management of the patient is influenced by diagnosis.

TABLE II. WHY BOTHER TO ESTABLISH DEFINITIVE DIAGNOSIS OF INFECTIONS?

Use of appropriate antimicrobial chemotherapy or chemoprophylaxis
Reduction of use, side effects, and expense of inappropriate therapy
Early implementation of surveillance and control measures: nosocomial or community based infections
Etiologic diagnosis: means for quality assurance control
Education: knowledge

tibody testing for the determination of respiratory syncytial virus antigen in nasopharyngeal smears.

Based on cost estimates in Children's Hospital Laboratories, the average cost of diagnostic tests for respiratory syncytial virus performed per patient is about $33.00. In view of the observations that respiratory syncytial virus infection is associated with hospitalization rates of up to 38/1000 infants/year and nosocomial infection rates of up to 30% during community outbreaks, laboratory diagnosis will be essential to screen children for hospitalization and to reduce the risk of nosocomial infection after hospitalization. Based on our experience at Children's Hospital of Buffalo, it would cost an additional $900 for each patient with nosocomial respiratory syncytial virus infection assuming that it will increase hospitalization for an existing inpatient by a minimum of two days and will necessitate other laboratory services. Thus, such nosocomial infections will cost an additional

TABLE III. AVAILABLE METHODS FOR DIAGNOSIS OF RESPIRATORY SYNCYTIAL VIRUS INFECTION

System	*Procedure*	*Speed*	*Cost*
Virus	Tissue culture infectivity	S	C++
	Immunofluorescent antibody of inoculated tissue culture	R	C++
Antigen	Immunofluorescent antibody	R	C+
	ELISA	R	C
	Electron microscopy	R	C++
Serology	Complement fixation	S	C−
	IgM, IgG, IgA	S	C
	Acute convalescent comparison	S	C−

R=relatively rapid, S=slow, C—low to ++ high= relative costs
Includes consideration for technical complexity and need for complex equipment.

TABLE IV. CORRELATION OF IMMUNOFLUORESCENCE ANTIBODY TO TISSUE CULTURE INFECTIVITY

		Nasopharyngeal smear immunofluorescent			
		*Respiratory syncytial virus***			
*Tissue culture infectivity**		*Positive*		*Negative*	
nasopharyngeal smears sample		*No.*	*%*	*No.*	*%*
Total number tested	693	199	29	494	71
Number positive	185	172	93	9†	4.8
Number negative	508	27	5.3	481	94

*Average time required for definitive identification—seven days
**Average time required for definitive identification—seven hours
†Four specimens unsuitable for IFA

$43,680 to the health care industry during each respiratory syncytial virus outbreak in Buffalo. This estimate is based on costs attributable to a minimum of 48 patients annually with nosocomially acquired infection (Table V). Therefore, it is suggested that laboratory diagnosis of respiratory syncytial virus may be cost effective in management and prevention of nosocomial infection.

Enzyme linked immunosorbent assay (ELISA) testing could be done in the physician's office. However, because of a certain amount of technical expertise required, seasonality of the infection, and changes in actual cost of the test relative to volume of samples, the cost effectiveness of shifting such testing to the physician's office needs to be determined. Immunofluores-

TABLE V. HEALTH CARE COST IMPACT OF NOSOCOMIAL RESPIRATORY SYNCYTIAL VIRUS INFECTION

Respiratory syncytial virus testing		*Minimal additional charges secondary to respiratory syncytial virus nosocomial infection*	*Average per patient*	*Average health care cost impact*
Cost/test				
High volume				
ELISA	19.50	Additional		
Immunofluorescent		hospital stay*	760	36,480
antibody	28.00			
Low Volume		Additional		
ELISA	32.00	lab test**	150	7,200
Immunofluorescent				
antibody	38.00			
Average	33.60	Total	910	43,680

Estimates based on 48 patients in Children's Hospital at Buffalo, 200 pediatric beds with 80% (160) occupancy in winter and at 30% respiratory syncytial virus nosocomial infection rate during community outbreak (=48)

*Hospital stay: 360 dollars/day in non-ICU facility

** Includes x ray and blood gases and additional medications

cent antibody procedures, because of their complexity, must remain within trained professional laboratory settings at this time.

Antiviral therapy is not indicated for the management of a routine respiratory syncytial virus infection. However, pulmonary (aerosol) therapy with Ribavirin at a dose of 0.82 mg/kg body weight per hour for an average of five days has been observed to result in significant improvement in clinical course of the disease, reduction in viral shedding, and improved pulmonary gas exchange. Of particular importance is the observation that no deaths were observed in respiratory syncytial virus infected patients with underlying heart disease or bronchopulmonary dysplasia after Ribavirin therapy. Such high risk patients may have an expected mortality of 8 to 30%.[8,9]

Since immunodeficiency or compromised immune status are seen more frequently because of therapeutically induced immunosuppression, the risk that respiratory syncytial virus infection will produce severe disease may exist in a much larger population of infants, especially those older than two years of age. Although data on Ribavirin therapy are based on relatively small number of patients to date, prevention or significant reduction in mortality associated with antiviral therapy is clearly an effective medical management.

Hopefully, in the future the cost of antiviral drugs such as Ribavirin will decline to affordable levels. The current costs of medication alone for a three-

TABLE VI. AVERAGE COST (IN U.S. DOLLARS) NECESSARY FOR TREATMENT OF HIGH RISK PATIENTS WITH RESPIRATORY SYNCYTIAL VIRUS INFECTION

Cost items	*Hospitalized*	*Not hospitalized*
Hospital stay/day	380	—
Lab tests and other expenses	150	33.60
Ribovirin cost/day	185	185.00
Total/day	735.00	218.60
Average cost for 5 days treatment	3 675.00	1 093.00*

*Does not include costs for home nursing care

day course is about $900. Estimates based on present day costs of Ribavirin suggest that inpatient, hospitalization-based aerosal treatment with Ribavirin will cost three times more than it would to provide the same therapy at home (Table VI). In view of the impact of nosocomial infections on hospital costs and the effectiveness of therapy in high risk groups, a strong case can be made for the cost effectiveness of both diagnosis and available treatment for respiratory syncytial virus infection.

Other Viruses

The implications of the rationale for diagnosis and treatment and the overview of the cost impacts for respiratory syncytial virus infection are applicable to viral diseases such as influenza, herpes simplex, and possibly other viruses.

Influenza. Influenza virus infection has an impressive record of mortality and morbidity for more than a century. The loss of earnings and production deficits associated with the 1968-69 influenza epidemic has been estimated to exceed 3 billion dollars. In terms of human deaths, it is estimated that the mortality associated with influenza virus infection during epidemics is approximately 10 per 100,000 population in otherwise healthy subjects more than 65 years of age. Mortality in high risk groups with cardiopulmonary disease is in the range of 100 to 1,000/100,000 population. Infection of this magnitude deserves adequate preparation both from diagnosis and management to lessen the economic and human impact of each epidemic or pandemic.[10]

Herpes simplex virus. While primary herpetic gingivostomatitis (HSV-1)

is not a disease of major magnitude, reactivation infection in vital tissues, encephalitis, and disseminated primary disease are important, although uncommon features of herpes simplex virus type I infection.[11] Similarly, relatively low mortality is associated with herpes simplex virus type II infection. However, considerable debate exists concerning its morbidity and economic impact. Approximately 600,000 new cases of genital herpes have been estimated for the years 1980-82, and cumulative episodes of recurrence have been put at 15 to 20 million/year. The risk of neonatal herpes is estimated to be about one in 3,000 births.[11]

Rapid laboratory diagnosis of herpes simplex virus, influenza, and other viruses is still neither available nor applicable on a routine basis. The tissue culture isolation procedures carried out traditionally for epidemiologic surveillance continue to remain the principal means of acquiring etiologic diagnosis. Identification of adenoviruses, herpes simplex virus, parainfluenza viruses, and influenza virus in tissue culture may take as long as four to 20 days. Although both immunofluorescent antibody and ELISA tests will provide results within hours, difficulties remain in achieving adequate sensitivity and specificity with the test procedures. With the introduction of monospecific reagents, especially monoclonal antibodies to HSV-I and HSV-II, it has been possible to achieve close to 93 to 98% correlation to tissue culture infectivity, for immunofluorescent antibody tests for DNA hybridization[12,13] for detection of herpes simplex virus in patient samples (Table VII).

The need for repeated testing for genital herpes simplex virus shedding by pregnant women prior to delivery is also debatable. It is believed that such testing may result in prevention of neonatal herpes simplex virus infection and the resultant loss or impairment of human function, since virus shedding women often elect cesarean delivery. However, no detailed cost effectiveness or risk versus benefit studies have been undertaken to determine the validity of this assumption. This is particularly important, since other epidemiologic studies have shown that only 15% of women evaluated for genital herpes simplex virus shedding within four weeks before delivery do in fact shed virus. On the other hand, 70% of women who have delivered an infant with neonatal herpes simplex virus infection do not exhibit signs or symptoms of genital herpes simplex virus infection, although most such women continue to shed virus for one to two months after delivery.[11]

At present there is no evidence of cost effectiveness in patient management for laboratory diagnosis for adenoviruses, parainfluenza viruses, and possibly influenza viruses.

Good evidence is available to suggest that prophylactic use of Amantidine

TABLE VII. IMMUNOFLUORESCENT ANTIBODY TESTING OF PATIENT SPECIMENS FOR DETECTION OF VIRAL ANTIGEN

Virus	*No. tested positive by tissue culture infectivity*	*Tested positive by immunofluorescent antibody test**	
		No.	*%*
Herpes simplex virus	15	14	93.3
Parainfluenza	11	9	81.8
Influenza	28	20	71.4

*Transit time between collection and testing <6 hrs.

begun early in the season will significantly reduce the risk of severe influenza in high risk patients and protection efficacy rates of as high as 60-100% have been reported in several carefully conducted studies.[10,14] In view of the high mortality of influenza among high-risk groups, such prophylactic use is cost effective. However, Amantadine is not effective against influenza B, and prolonged therapy for a large population over time may not be cost effective. Thus the use of Amantidine may be justified only for high risk people, especially as household contacts exposed to the virus without vaccine protection.

The experience with antiviral therapy in herpes simplex virus infection is better defined than with other agents as reviewed recently.[11] Use of Acyclovir administered intravenously more than five to seven days has been found to reduce the mortality of herpes simplex virus encephalitis by 50 to 70% in immunologically normal hosts. Significant reduction in mortality and morbidity has also been observed in primary neonatal and genital herpes simplex virus infection treated with acyclovir. Although use of acyclovir will significantly reduce the frequency of recurrences in herpes simplex virus infection,[15] the impact of such long-term therapy on reducing the incidence of neonatal herpes simplex virus infections or increasing the potential for emergence of acyclovir resistant viral strains has not been determined.

SUMMARY

Specific etiologic diagnosis of infections is an important tool for careful monitoring and early implementation of surveillance and control measures for management of nosocomial and community-based viral infections. Recent developments in rapid diagnosis and availability of several helpful antiviral chemotherapeutic agents have significantly altered the management of infections with respiratory syncytial virus, herpes simplex virus, and to a smaller extent for infections with influenza and parainfluenza viruses. Such

diagnostic and therapeutic approaches have resulted in use of appropriate antiviral chemotherapy in high risk patients with respiratory syncytial or herpes simplex virus infection, reduction in use, side effects and expense of unnecessary antibacterial chemotherapy, and increased efficacy of hospital-based quality control measures. Such an approach represents the most effective means to acquire knowledge concerning specific viral diseases. Available diagnostic methodology, although expensive, appears to be cost effective in terms of short and long-term financial impact to the community resulting from morbidity and mortality associated with these viral infections.

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